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Mast cell activation syndromes

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Target Audience: Physicians involved in providing patient care in the field of allergy/asthma/immunology
Learning Objectives:
At the conclusion of this activity, participants should be able to:

- Describe the classification of mast cell activation disorders with emphasis on monoclonal mast cell activation syndrome (MMAS) and idiopathic mast cell activation syndrome (MCAS)
- Discuss the clinical presentations, evaluation, diagnostic approach and management of MMAS and MCAS disorders

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Table 1
Global classification of mast cell activation diseases[7]

Classification	Diseases
Primary	Mastocytosis (systemic or cutaneous)
	Monoclonal mast cell activation syndrome
Secondary	Allergic diseases
	Mast cell activation–associated chronic inflammatory or neoplastic disorders
	Physical urticarias
	Chronic autoimmune urticaria
Idiopathic	Mast cell activation syndrome
	Idiopathic anaphylaxis
	Idiopathic urticaria
	Idiopathic angioedema (with or without urticaria)

Case Presentation

A 50-year-old woman with a 10-year history of episodic flushing and abdominal cramps with diarrhea that have increased in frequency during the last few months was initially evaluated in the office. Since the age of 40 years, she had symptoms that occurred every few weeks to every few months, lasting minutes to hours. She felt fatigued for a few days after the episodes but was well otherwise between the events. On further questioning, she reported 2 episodes of syncope with documented hypotension that required fluid boluses and intramuscular epinephrine in the emergency department. One of the episodes occurred after spending hours under the sun while gardening. She was evaluated by an endocrinologist for these episodes of flushing and had normal 24-hour urinary 5-hydroxyindoleacetic acid, fractionated metanephrine, and normetanephrine levels. She was also seen by a gastroenterologist for evaluation of her abdominal symptoms and had an endoscopy and colonoscopy performed, which produced unremarkable gross and histopathologic results. Her family history was noncontributory. Her social history was unremarkable. She denied medication allergies and was not taking any medications on a daily basis. Her vital signs were stable, and physical examination findings were unremarkable without evidence of urticaria pigmentosa (UP). The baseline tryptase level was 7 ng/mL during the initial evaluation. Another tryptase sample was drawn after one of the described episodes, which revealed a level of 18 ng/mL. Because of her documented history of hypotension and syncope, bone marrow aspirate and biopsy were performed, which revealed normal trilineage maturation and scattered mast cells without significant clustering. Approximately 20% of the mast cells had elongated morphologic findings on tryptase staining. The flow cytometry of the aspirate revealed too few mast cells to evaluate. However, immunohistochemical analysis revealed aberrant CD25 expression on mast cells. The result of c-kit mutational analysis of the bone marrow aspirate was positive for D816V point mutation. The patient was diagnosed as having monoclonal mast cell activation syndrome (MMAS) and was given histamine$_1$ (H_1) and histamine$_2$ (H_2) blockers twice daily with improvement in her symptoms. Subsequently, she was given cromolyn sodium for worsening abdominal cramps. During her subsequent yearly follow-up, she reported a notable decrease in the frequency (to less than once per month) and severity of her episodes. She would still experience some flushing and mild abdominal cramping, but the episodes would not progress to anaphylaxis.

Table 2
World Health Organization criteria for systemic mastocytosis[a,3]

Criterion	Description
Major	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in biopsy specimens of bone marrow and/or extracutaneous organs
Minor	1. Abnormal morphologic findings in >25% of mast cells in bone marrow or extracutaneous organs via smear or histologic analysis
	2. Expression of CD2 and/or CD25 on mast cells
	3. c-kit mutation at codon 816 in lesional tissue
	4. Serum total tryptase >20 ng/m: (not valid if there is an associated hematologic disorder)

[a]Diagnosis of systemic mastocytosis can be made if major criterion and at least 1 minor criterion or at least 3 minor criteria are fulfilled.

Classification and Diagnostic Criteria

Mast cell activation diseases (MCADs) are a collection of disorders that usually present with recurrent signs and symptoms of mast cell mediator release, such as flushing, abdominal cramps, and hypotension. A 2010 proposal for classification divides them into 3 categories: primary (clonal), secondary (nonclonal), and idiopathic (unknown whether clonal or nonclonal) (Table 1). The clonal disorders are those in which there is an inherent defect in the mast cells and their progenitors (such as D816V c-kit mutation, a single base pair substitution from aspartic acid [D: wild type] to valine [V: mutant] in tyrosine kinase at codon 816 in mast cells and their progenitors), presumably reducing their activation threshold. Such disorders include systemic mastocytosis (SM) and MMAS. The nonclonal disorders include a broader variety of more common diagnoses, which can be secondary to allergic diseases, physical or chronic urticaria, chronic inflammation, neoplastic processes, and idiopathic mast cell activation syndrome (MCAS), as well as all cases of idiopathic anaphylaxis.[7,10] Other classification schemes have also been proposed.[9] Because detailed reviews of mastocytosis and individual disease states causing secondary mast cell activation are widely available, we focus our discussion on MMAS and idiopathic MCAS.

MMAS is part of the clonal classification that demonstrates aberrant genetic and surface markers that are intrinsic to mast cells. Unlike SM, patients with MMAS do not present with UP and often present with a normal baseline tryptase measurement that can increase during symptomatic episodes. MMAS does not fulfill the World Health Organization diagnostic criteria for SM but displays 1 or 2 minor criteria (such as c-kit mutation or CD25 expression on bone marrow analysis) (Table 2). If all 3 minor criteria are met, then the diagnosis of SM should be made.[1–3]

Idiopathic MCAS is a disorder in which no clonal markers (such as c-kit D816V mutation or CD25-positive mast cells) have occurred. The proposed international consensus criteria state the patient should meet all of the following 3 criteria (Table 3): (1) recurrent clinical manifestations of mast cell hyperreactivity, (2) laboratory results showing validated markers of mast cell activation (such as serum tryptase or urinary N-methylhistamine, prostaglandin D_2, or 11-β-prostaglandin F2α), and (3) improvement in symptoms with medications that target these mediators. Like MMAS, MCAS also does not present with UP. The distinction from MMAS is that patients with MCAS do not demonstrate any of the clonal markers for SM. Some patients with MCAS may have slightly elevated baseline tryptase levels (up to approximately 30-35 ng/mL in some patients), and some episodes may also meet the criteria for idiopathic anaphylaxis, although not all episodes progress into anaphylaxis with cardiac or respiratory compromise[7,8,10] Hamilton et al[8] prospectively studied 18 patients diagnosed as having MCAS. All patients in this series fulfilled the previously stated proposed diagnostic criteria, and most of these patients exhibited abdominal cramps, dermatographism, and flushing.[8] Patients showed excellent response to antimediator therapy, such as long-term scheduled combination of H_1- and H_2-antihistamines and/or oral cromolyn sodium.

Clinical Manifestations

Clinical presentations of both MMAS and MCAS generally include recurrent signs and symptoms of mast cell mediator release

Table 3
Diagnostic criteria for mast cell activation syndrome[a,7,10]

1. Signs and symptoms of mast cell activation involving at least 2 organ systems (eg, gastrointestinal: abdominal cramps, diarrhea; respiratory: bronchospasm;
cardiovascular: hypotension or syncope; and skin: flushing, itching and less commonly urticaria and angioedema)
2. Increase in release of mast cell markers, such as tryptase, 24-hour urine histamine metabolites, or prostaglandin D_2 or its metabolite (11-β-prostaglandin F_2) with symptoms
3. Response in clinical symptoms to antimediator therapy

[a]The proposed international consensus criteria for mast cell activation syndrome should meet all of these 3 criteria.

involving at least 2 organ systems. These systems include gastrointestinal, skin, respiratory, cardiovascular, musculoskeletal, and/or neurologic systems. Both disorders can manifest a wide variety of symptoms, including abdominal cramps, diarrhea, urticaria, bronchospasm, hypotension, or syncope, although urticaria and angioedema are less common presentations of MMAS as opposed to MCAS. In contrast, anaphylaxis with hypotension is more common in clonal mast cell disorders (ie, MMAS or SM). Triggers of these signs and symptoms include external stimuli, such as medications, alcohol, and Hymenoptera stings, as well as emotional stress.

Although all mast cell activation diseases can present with similar symptoms of mast cell mediator release, there are unique features in terms of signs and symptoms, physical examination findings, and diagnostic test results that help differentiate clonal and nonclonal subtypes. Anaphylaxis to Hymenoptera stings should raise suspicion for *clonal* mast cell activation diseases. A study by Bonadonna et al[4] found that 13.8% of patients with anaphylaxis to Hymenoptera stings had underlying clonal mast cell activation disorders. More specifically, 29 of 31 patients (89%) who presented with both an elevated serum tryptase level (>11.4 ng/mL) and a history of anaphylaxis to Hymenoptera sting showed clonal abnormality consistent with either indolent SM or MMAS. In addition, a study by Alvarez-Twose et al[6] suggests a model to predict clonality. The independent factors in this model include male sex, syncopal-like episode without accompanying urticaria and angioedema, and tryptase level greater than 25 ng/mL. Presence of UP skin lesions should point to a diagnosis of SM or cutaneous mastocytosis rather than other types of MCAD.[2,4,6]

Another subset of the population that should be considered for diagnosis of clonal MCAD includes patients with idiopathic anaphylaxis. One study found that 5 of 12 patients diagnosed as having idiopathic anaphylaxis fulfilled 1 or more minor criteria for the diagnosis of SM. Specifically, all 5 patients had positive c-kit mutation analysis results, and 3 of the 5 patients also expressed CD25. Therefore, patients with recurrent unexplained anaphylaxis without known triggers should be carefully evaluated for clonal mast cell activation disorders.[2]

Diagnostic Approach

The patients with SM usually present with elevated baseline tryptase levels (>20 ng/mL), whereas patients with MMAS and MCAS usually present with normal or slightly elevated baseline tryptase levels less than 20 ng/mL. In terms of patients with venom anaphylaxis, a tryptase level less than 11.4 ng/mL appears to help differentiate nonclonal from clonal disease in most patients. However, elevations in tryptase level during symptomatic episodes are possible and are confirmatory of mast cell activation.[16] Total tryptase is the sum of mature protryptases that can be measured in commercial laboratories. During a symptomatic episode, a significant elevation of tryptase would be a level of 20% above the baseline plus 2 ng/mL. For example, if the baseline value was 10 ng/mL, a level of 14 ng/mL or above would be considered significant. In addition, although tryptase elevation in symptomatic episodes is the most specific marker of mast cell activation, elevation of 24-hour urine *N*-methylhistamine, prostaglandin D_2, or 11-β-prostaglandin F2 also suggests mast cell activation. Patients with MMAS demonstrate abnormal genetic or phenotypic expression in the bone marrow, such as mutation of c-kit codon 816 and/or surface marker expression of CD25 on mast cells. The finding of similar abnormal markers of mast cells in extracutaneous tissues (such as gastrointestinal biopsies) is also acceptable evidence of clonality but less commonly detected.[1,3,6,7,10,15]

Management

The management of patients with mast cell activation diseases includes medications that mainly target the effects of mast cell mediators. The initial approach includes nonsedating H_1-antihistamines (eg, cetirizine, fexofenadine, and loratadine) that can be titrated up to twice daily dosing for prophylaxis and overall symptom control. If urticaria is a prominent symptom, increases up to 4 times the recommended dose have been used. An addition of first-generation H_1-antihistamine (such as diphenhydramine or hydroxyzine) can be used for breakthrough symptoms of urticaria or pruritus. For further control of abdominal symptoms, H2-antihistamines can be added (such as ranitidine and famotidine) at twice-daily dosing. In case of persistent symptoms, addition of ketotifen, 1 to 2 mg every 12 hours (not available in the United States), or cromolyn sodium, which is usually prescribed as 800 mg/d in 4 divided doses, can be considered. Furthermore, both montelukast, 10 mg once at night, and aspirin are helpful in managing the effects of arachidonic acid metabolites. We usually start with 81 mg/d of aspirin, and if tolerated this is increased gradually up to 325 mg twice daily in patients who are known not to be allergic or intolerant of nonsteroidal anti-inflammatory drugs. Gastric protection is prescribed concurrently. Patients with anaphylactic episodes and all patients with clonal mast cell disease, regardless of history of anaphylaxis, should be prescribed multiple units of self-injectable epinephrine and educated on proper use of the device. Although these medications may not completely eliminate the symptoms, improvement in severity, duration, or frequency of symptoms is expected.[11–14]

Prognosis

Similar to patients with indolent SM, patients with MMAS and MCAS likely have a comparable life expectancy to that of the general population.[5] Fatalities have been reported in patients with clonal mast cell disorders after Hymenoptera stings. Therefore, most experts agree that such patients with underlying mast cell disease should be treated with lifelong venom immunotherapy if they test positive for venom specific IgE. In our experience, although most patients with venom anaphylaxis have either skin or blood test evidence of venom specific IgE, some patients do not. Repeating allergy testing is recommended in these patients in approximately 6 months. There is no consensus on whether to empirically initiate venom immunotherapy in this population. It should be kept in mind that these patients are also more likely to experience systemic reactions during venom immunotherapy and the degree of protection from sting anaphylaxis is less than individuals without mast cell disorders.[1,4]

Conclusion

Patients with mast cell activation diseases are often evaluated by multiple specialists before diagnosis. The clinical manifestations that involve multiple organ systems and demonstrate the effects of mast cell mediators should prompt physicians to include MCAS and MMAS, in addition to SM, as part of their differential diagnoses. Patients with baseline tryptase levels greater than 11.5 ng/mL or

significant elevation of their baseline tryptase levels during symptomatic periods, hypotensive anaphylactic episodes, or anaphylactic Hymenoptera hypersensitivity are candidates for more aggressive diagnostic approaches, such as bone marrow biopsy, to look for evidence of clonal mast cell disease, such as SM or MMAS.

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